REMARKS

Upon entry of the instant amendment, claim 1 will be amended, whereby claims 1, 2 and 4-26 will remain pending. Claim 1 is the sole independent claim.

Claim 1 is amended herein in accordance with proposed amendments thereto as discussed with the Examiner during an interview which will be discussed below. Entry of this amendment is made because it even further clarifies Applicants' claimed invention. Moreover, entry is appropriate because of the finality of the Office Action is premature for the reasons that are discussed in the arguments below.

Reconsideration and allowance of the application are respectfully requested.

Discussion Of December 2, 2003 Interview

Applicants express appreciation for the courtesies extended by Examiners Long Le and Gary Counts at a personal interview with Applicants' representative Arnold Turk on December 2, 2003 at the Patent and Trademark Office.

During the interview, Applicants' invention and the prior art, including the "Background Art" section of the specification and Applicants' contribution thereto, were thoroughly discussed along with proposed amendments to claim 1 to even further clarify the terminology therein.

The proposed amendment to claim 1 is included in the amendment herein which is being made to even more clearly denote the terminology utilized in the claims in accordance with the discussion of such terminology in the specification, such as appearing in the originally filed specification at the bottom of page 4 through the middle of page 5, and especially page 5, the

second full paragraph.. In particular, as discussed with the Examiners, Applicants agreed to amend claim 1 to clearly define that the ligand bonded complex has affinity for both non-free and free target but specifically binds to the non-free in the presence of both a non-free target and a free target.

In particular, during the interview, the Examiners contended that Buechler taught a microparticle with a ligand on its surface that would bind to a complex or a free form of troponin. Arguments were presented that in accordance with Applicants' invention a ligand having an affinity for both a free target and a non-free target so that the free target can generally be recognized by the ligand at a substantially equivalent level as the non-free target when not bound to a microparticle is included in a ligand-bonded complex comprising a microparticle directly or indirectly bonded to the ligand. Arguments were also presented that plural numbers of the ligand are bond to a surface of the microparticle thereby increasing affinity of the at least one ligand to the non-free target, and that the increasing affinity of the at least one ligand bond to a surface of the microparticle allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target.

The Examiners asserted that number of ligands can be determined by optimization and that Buechler teaches the use of different antibody, and arguments were presented in response thereto.

Moreover, arguments were presented regarding the other documents utilized in the rejection of record including emphasizing arguments presented in the immediately previously submitted response.

Still further, Applicants presented arguments that the finality of the rejection was premature because of the use of Tagawa in the rejection of claims 2 and 7. The Examiners agreed to consider this issue if raised in the response.

Arguments as presented during the interview are included in the remarks herein.

Rejections Based Upon Prior Art

The following rejections are set forth in the Final Office Action:

(a) Claims 1, 4-6, and 8-15, 19, 21-23, 25 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Allen et al. (hereinafter "Allen"), U.S. Patent No. 5,527,528.

(b) Claims 1, 4, 9, 13, 16, and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Buechler et al. (hereinafter "Buechler"), U.S. Patent No. 6,156,521.

(c) Claims 2, 7, 20 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen, U.S. Patent No. 5,527,528, in view of Tagawa et al. (hereinafter "Tagawa"), U.S. Patent No. 5,264,221.

(d) Claims 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buechler, U.S. Patent No. 6,156,52, in view of Nichtl et al. (hereinafter "Nichtl"), U.S. Patent No. 5,972,720.

(e) Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Allen, U.S. Patent No. 5,527,528, in view of Lindhofer et al. (hereinafter "Lindhofer"), U.S. Patent No. 6,294,127.

Request For Withdrawal Of Finality Of Office Action

As discussed with the Examiners during the above-noted interview, rejection (c), i.e., the rejection of claims 2, 7, 20 and 24 under 35 U.S.C. 103(a) as being unpatentable over Allen in view of Tagawa, was not included in the previous Office Action, and is raised upon unamended claims in the present Final Office Action. The Examiner is reminded that, under present Patent and Trademark Office practice, an Office Action should not be made final where the examiner introduces a new ground of rejection therein that is neither necessitated by Applicants' amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p). Therefore, this new ground of rejection was not necessitated by Applicants' amendment. Accordingly, the finality of the Office Action is premature, and should be withdrawn in the event that the application is not allowed in response to the instant response.

Response To Rejections

In response to the rejections of record, Applicants respectfully submit the following.

Initially, Applicants point out that their invention, as recited in independent claim 1, is directed to a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least one ligand, the ligand having an affinity for both a free target and a non-free target so that the free target can generally be recognized by the ligand at a substantially equivalent level as the non-free target when not bound to the microparticle, the at least one ligand comprising plural numbers of the at least one ligand bond to a surface of the microparticle thereby increasing affinity

of the at least one ligand to the non-free target, wherein the increasing affinity of the at least one ligand bond to a surface of the microparticle allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target.

As discussed with the Examiners during the above-noted interview and as set forth in Applicants' specification in the Background Art section, targeting therapies using antibody-bonded complexes are based on high specificity of the ligand to a target, and therefore, superior therapeutic effect and reduced side effect can be expected. It is disclosed that in the targeting therapy, a problem has been pointed out in that an antibody-bonded complex reacts with a free target such as a free antigen existing in blood or the like, and thus a sufficient amount of the drug cannot react with a solid tumor tissue, including a primary lesion and a metastatic foci, having non-free antigens and the like. In other words, it is disclosed that when a part of antigens are secreted into blood or antigens are released from cancer cells free antigens (soluble antigens) appear in blood, as observed in certain types of cancers, antibody-bonded complexes will react with the free antigens to form immuno-complexes, thereby the reaction with target cells will be inhibited. Accordingly, it is disclosed in order to design an antibody-bonded complex, it is generally required to chose an antibody whose antigen is absent or at an extremely low level in blood. Further, it is disclosed than an antibody against an antigen, whose significance in serum diagnosis has been established clinically, is impossible to use in the manufacture of an antibody-bonded complex.

As disclosed in the "Disclosure of the Invention: section of Applicants' specification, in order to solve the aforementioned problems, the inventors of the present invention conducted

researched on the relationship between soluble target substances, such as a free antigen and ligands, such as an antibody. Surprisingly, it was found that a ligand-bonded complex, to which plural numbers of a ligand having low affinity to a target substance were bonded, had a high reactivity to a non-free target, such as a cancer cell, even in the presence of a free target substance.

From the above, it is apparent that, in the prior art, a particular kind of antibody is selected so as to be able to bind to non-free target, but not bind to free-target. In contrast, according to the present invention, an antibody having affinity both for non-free target and free target is used, and by using plural numbers of the antibody, a selective affinity for the no-free target is achieved.

During the above-noted interview, the Examiners discussed examples of systems wherein different antibodies interacted with different substances. Moreover, in discussing each of Buechler. and Allen, the Examiners made similar arguments that different antibodies can interact with different substances. Specifically, the Examiners were arguing that different antibodies react with the different substances, and therefore the antibodies are specific to different substances. In contrast, arguments were presented that according to Applicants' invention the ligand generally has affinity to both non-free target and free target, but specifically binds to the non-free target. The Examiners argued that it would have been obvious to optimize the ligands by varying their number, and that affinity can be increased by increasing the number of ligands on the microparticle. However, in contrast to these assertions, the prior art of record does not teach or suggest that there can be specific binding of a ligand to non-free target in the presence of free target.

Regarding the prior art utilized in the rejections of record, Applicants respectfully submit that neither Allen nor Buechler discloses each and every element of the claimed invention.

Moreover, any modification of Allen or Buechler, as asserted in the rejections of record, would not arrive at Applicants' disclosed and claimed invention. Accordingly, the rejections are without appropriate basis and should be withdrawn. In particular, the prior art of record whether taken alone or in combination does not teach or suggest a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least one ligand, the ligand having an affinity for both a free target and a non-free target so that the free target can generally be recognized by the ligand at a substantially equivalent level as the non-free target when not bound to the microparticle, the at least one ligand comprising plural numbers of the at least one ligand bond to a surface of the microparticle thereby increasing affinity of the at least one ligand to the non-free target, wherein the increasing affinity of the at least one ligand bond to a surface of the microparticle allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. For the sake of brevity, Applicants are not repeating previously presented arguments, but are instead referring to their previously presented arguments including the arguments presented in their response filed June 16, 2003.

Regarding the rejections based upon Allen, the Office Action responds to Applicants' arguments by asserting that Allen discloses a monoclonal antibody which is specific for an antigen on highly proliferating cells in lung squamous carcinoma (non-free target). The Office Action asserts that in view of this highly specific binding of the monoclonal antibody, it would only bind to the non-free target. The Examiner contends that should there be any free target present, it would only bind to the non-free target. However, this is different from the invention as recited in Applicants' claims including, amongst other features, a ligand having an affinity for both a free

target and a non-free target so that the free target can generally be recognized by the ligand at a substantially equivalent level as the non-free target when not bound to the microparticle, the ligand comprising plural numbers of the at least one ligand bond to a surface of the microparticle thereby increasing affinity of the at least one ligand to the non-free target, and the increasing affinity of the at least one ligand bond to a surface of the microparticle allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target.

Further, with regard to arguments relating to the administration of multivalent species to accelerate clearance of nonspecifically-bound antibodies from the bloodstream, the Office Action contends that this relates to a different embodiment than that utilized in the rejection. However, this is another illustration that the prior art does not teach or suggest increasing affinity of a ligand bond to a surface of a microparticle allowing specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. For example, Allen appears to disclose specificity with respect to tumor epitopes of interest without regard to their status as free or non-free.

Regarding the rejections based upon Buechler, the Office Action refers to Buechler column 18, lines 6-65, and alleges that the antibodies coupled to a signal generator of Buechler bind to the troponin complexes or to the uncomplexed troponin T and I (free target), and asserts that Buechler therefore reads on the claimed invention. However, the disclosure of Buechler relates to use of different materials specific to different substances, and not complexes as recited in Applicants' claims including the recited ligand characteristics. For example, at column 11, line 13 et seq.,

Buechler discloses that:

> One skilled in the art will also recognize that antibodies with different affinities that is, exhibit different assay responses, for the troponin forms can also be utilized in immunoassays when each troponin form is measured alone or in discrete zones and that the relative bias of the immunoassays can be accounted for in the calibration of the assay. Also, sensitive and insensitive antibodies can be attached to solid phases to measure each troponin form in discrete zones.

Moreover, at column 18, line 46 et seq., Buechler discloses that:

> One skilled in the art will realize that increasing concentrations of all the troponin components in the blood will result in an increasing fraction of bound troponin I and T relative to free troponin. The concentration of total troponin (bound and free) may rise faster than the concentration of free troponin I and T. An assay that measures the total troponin concentration (bound and free troponin I and T) would be more accurate in assessing progression of heart damage as compared with an assay that measures only free troponin I or T.

A review of the total disclosure of Buechler reveals that Buechler does not teach or suggest, amongst other features, a ligand having an affinity for both a free target and a non-free target so that the free target can generally be recognized by the ligand at a substantially equivalent level as the non-free target when not bound to the microparticle, the ligand comprising plural numbers of the at least one ligand bond to a surface of the microparticle thereby increasing affinity of the at least one ligand to the non-free target, and the increasing affinity of the at least one ligand bond to a surface of the microparticle allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target.

The remaining references modify Allen or Buechler in an attempt to arrive at Applicants' invention as further defined in their dependent claims. However, these references do not overcome the deficiencies of Allen or Buechler. Therefore, any modification of Allen or Buechler, whether

or not there is any motivation in the prior art to make the modification asserted in the rejections, would not arrive at Applicants' invention.

In particular, with regard to Tagawa, the rejection asserts that it would have been obvious to one of ordinary skill in the art to incorporate polyalkylene glycol as taught by Tagawa with the liposome of Allen because Tagawa shows that the use of polyalkylene glycol provides a drug-containing antibody-bonded liposome having the nature of being captured in the reticuloendothelial system improved. However, whether or not it would have been obvious to modify Allen in the manner asserted in this rejection, Applicants' invention would not be at hand.

Moreover, the rejection asserts that it with respect to the number of ligands bonded to the microparticle, the optimum number of ligands can be determined by routine experimentation because it would have been obvious to optimize a result effective variable. However, in contrast to this assertion, there is no teaching or suggestion in the prior art of, amongst other features recited in Applicants' claims, a ligand having an affinity for both a free target and a non-free target so that the free target can generally be recognized by the ligand at a substantially equivalent level as the non-free target when not bound to the microparticle, the ligand comprising plural numbers of the at least one ligand bond to a surface of the microparticle thereby increasing affinity of the at least one ligand to the non-free target, and the increasing affinity of the at least one ligand bond to a surface of the microparticle allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. Accordingly, there is no teaching or suggestion of performing experimentation in any manner associated with Applicants' invention.

The rejections further assert that Nichtl discloses and motivates one skilled in the art to incorporate polyethylene glycol into the ligand complex of Buechler. For the sake of brevity, arguments in this regard are not being expanded upon herein, because of the deficiencies associated with any combination of the disclosures of these documents. In particular, the above noted deficiencies of Buechler are not in any manner overcome by any disclosure of Nichtl. Accordingly, this ground of rejection should also be withdrawn.

Moreover, the rejections further assert that Allen does not disclose a pharmaceutical composition, but that Lindhofer discloses such and motivates its use in Allen. In response, Applicants respectfully submit that there is no motivation to combine the disclosures of Allen and Lindhofer. However, for the sake of brevity, arguments in this regard are not being expanded upon herein, because of the deficiencies associated with any combination of the disclosures of these documents. In particular, the above noted deficiencies of Allen are not in any manner overcome by any disclosure of Lindhofer. Accordingly, this ground of rejection should also be withdrawn.

Thus, Applicants respectfully submit that Applicants' claims patentably define their invention, whereby withdrawal of the rejections of record is respectfully requested.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the objections and rejections of record, and allow all the pending claims.

Allowance of the application is requested, with an early mailing of the Notices of Allowance and Allowability.

If the Examiner has any questions or wish to further discuss this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
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